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16. (Amended) The monoclonal antibody of claim 1 which binds to the same domain of TIP-2 as does monoclonal antibody 27.F7.

REMARKS

Claims 1-18 are pending. By this Amendment, applicants have amended claims 6 and 16 to incorporate minor grammatical changes. No claim has been added or cancelled. Accordingly, claims 1-18 will still be pending and under examination upon entry of this Amendment.

Objections to the Specification

On page 2 of the September 26, 2002 Office Action, the Examiner stated that the disclosure is objected to because of informalities which required the following corrective actions: missing ATCC numbers should be added; claim numbers should not be referenced in the specification because the numbers can be changed during prosecution; SEQ ID Nos. should be added to the sequences in the specification; the NIH grant no. missing from page 1, line 2 should be provided; and the ATCC address on page 39, lines 17-19 should be updated.

In response, applicants have hereinabove amended the specification to address the Examiner's remarks.

The Examiner also stated that the title of the invention is not descriptive and a new title is required that is clearly indicative of the invention to which the claims are directed.

In response, applicants have amended the title hereinabove. Applicants maintain that the new title is clearly indicative of the invention to which the claims are directed.

Claim Rejections under 35 U.S.C. §112, First Paragraph

Claims 1-18

The Examiner stated that claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public, and (2) reproducible from the written description. The Examiner further indicated that deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. 112, first paragraph, in accordance with 37 C.F.R. 1.801-1.809.

In response, applicants state that the hybridomas producing the antibodies designated 27.F7 and 27.B1 have been deposited pursuant to the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure with the Patent Culture Depository of the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, VA 20110-2209, U.S.A., under ATCC Designation Nos. PTA-1598 and PTA-1599, respectively. Applicants attach hereto as **Exhibit C** a copy of the Budapest Treaty Deposit Receipt and Viability Statement for the hybridoma cells producing the antibodies designated 27.F7 (ATCC No. PTA-1598) and 27.B1 (ATCC No. PTA-1599).

As confirmed by the Budapest Treaty Deposit Receipt and Viability Statement, all restrictions upon public access to the materials deposited under ATCC Nos. PTA-1598 and PTA-1599 will be irrevocably removed upon the grant of a patent on this application. The deposits will be maintained by the ATCC for a period of 30 years from the date of deposit or at least five years after the last request for a sample of the deposited material, whichever is longer. Where the ATCC cannot furnish samples of the above deposits for any reason, applicants shall make a replacement deposit of the material which was originally deposited within three months of receiving notification that the ATCC cannot furnish samples.

In view of the foregoing, applicants request that the Examiner withdraw the rejection of claims 1-18 under 35 U.S.C. 112, first paragraph.

Claims 6 and 16

The Examiner rejected claims 6 and 16 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In response to the Examiner's rejection of claims 6 and 16, applicants respectfully traverse.

The Examiner stated that the claims are broadly drawn to an antibody which binds to the same TIP-2 epitope as 27.B1 and 27.F7 but that the specification fails to enable the epitope to which

the antibodies bind.

Relying on Greenspan et al. (Nature Biotechnology 7:936-937 (1999)), the Examiner asserted that epitopes are defined in terms of the spatial organization of residues that make contact with a ligand, and further that epitope boundaries are defined by the structural characterization of the molecular interface for the binding of the molecules. According to the Examiner, an epitope defined in this manner will likely include residues that contact the ligand but are energetically neutral or even destabilizing to binding, and a priori will not include any residue that makes no contact with a ligand but whose substitution may profoundly affect ligand recognition through influence on the stability of the free form of the macromolecule, or participation in long-range allosteric effects. The Examiner stated that Westhof et al. (Nature 311:123-126, 1984) also teach the difficulty of defining epitopes, especially conformationally dependent epitopes. The Examiner concluded that due to the unpredictability of defining the epitopes to which antibodies bind as evidenced from Greenspan et al. and Westhof et al. and in view of the lack of guidance and examples in the specification, one skilled in the art would not know how to practice the broadly claimed invention without undue experimentation.

In response, applicants maintain that the purported difficulty of defining an epitope at the molecular level in terms of the residues that make contact with the antibody in a thermodynamically favorable way, or that otherwise enhance binding to the antibody, is irrelevant to claims 6 and 16. Applicants point out that, indeed, the term "epitope" does not appear in the rejected claims as amended. Notwithstanding that fact, one skilled in the art would immediately appreciate that

epitopes can be readily distinguished using a combination of techniques that are well-known in the art, such as competitive binding assays. For the purposes of claims 6 and 16, therefore, rather than unambiguously defining the epitope at the molecular level which is the difficulty addressed by Greenspan et al. and Westhof et al., it suffices that the particular epitopes to which antibodies 27.B1 and 27.F7 bind can be readily distinguished from other epitopes by known techniques.

In view of the above remarks, applicants respectfully request that the Examiner reconsider and withdraw the rejections of claims 6 and 16 under 35 U.S.C. 112, first paragraph.

Claim Rejections under 35 U.S.C. §103(a)

Claims 1, 2, 8 and 10-15

The Examiner rejected claims 1, 2, 8 and 10-15 under 35 U.S.C. §103(a) as allegedly unpatentable over De Vries et al. (PNAS 95: 12340-12345, 1998) and Rousset et al. (Oncogene 16: 643-654, 1998) and as evidenced by the specification, and further in view of Campbell (Monoclonal Antibody Technology, Elsevier Science Publishers, pages 1-32, 1986) and Harlow et al. (Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, page 322, 1988) of record.

In response to the Examiner's rejection of claims 1, 2, 8 and 10-15, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness of claims 1, 2, 8 and 10-15 for the following reasons.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim: firstly, that the cited references, when combined, teach or suggest every element of the claim; secondly, that one of ordinary skill in the art would have been motivated to combine the teachings of the cited references at the time of the invention; and thirdly, that there would have been a reasonable expectation that the claimed invention would succeed.

According to the Examiner, the rejected claims recite a monoclonal antibody that binds to TIP-2 and the antigen recognized by the antibody 27.B1 and 27.F7, wherein the antibody is a murine antibody, wherein the antibody is labeled with a radioactive isotope for imaging and therapy. The Examiner stated that De Vries et al. and Rousset et al. both teach the TIP-2 protein, and whereas these references do not teach a monoclonal antibody to TIP-2 or a labeled antibody, these deficiencies are made up for by Campbell and Harlow et al. which teach the production of murine monoclonal antibodies and labeling methods for detection respectively. The Examiner concluded that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a monoclonal antibody to the protein of De Vries et al. and Rousset et al. by the method of Campbell, and to label the antiboby as taught by Harlow et al.

In response, applicants note that the claims in fact provide a monoclonal antibody that binds to TIP-2 antigen <u>located on the surface of human cancer cells</u> and to the same antigen recognized by antibodies 27.B1 and 27.F7. Thus, the claims are not merely to an antibody that binds to TIP-2 antigen, but rather to one that binds to TIP-2 antigen specifically associated with the

surface of tumor cells. This element of the claims is not taught in any of the cited references, and therefore a *prima facie* case of obviousness cannot be established when, as here, it is clear that not all elements of the claims are taught by the cited references.

Moreover, applicants submit that there was no motivation to combine the teachings of the cited references at the time of the invention to produce monoclonal antibodies that bind to tumor-specific antigens. The Examiner quoted Campbell that "[i]t is customary for any group working on a macromolecule [in this case, TIP-2] to both clone the genes coding for it and to make monoclonal antibodies to it (sometimes without a clear objective for their application)." The Examiner therefore alleged that one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a monoclonal antibody to the protein of De Vries et al. and Rousset et al. by the method of Campbell, and to label the antibody as taught by Harlow et al.

In response, applicants disagree on the ground that a generic statement of what is a frequently used experimental approach cannot reasonably be construed as motivation for carrying out the specific set of experiments leading to the isolation of monoclonal antibodies that bind to distinct domains of a particular, tumor-associated antigen. Applicants contend that monoclonal antibodies are but one of many tools utilized in studying a protein, and while the production of such antibodies is not uncommon, it is certainly not de rigueur. Indeed, although, as the Examiner notes, TIP-2 had previously been described by De Vries et al. and Rousset et al., the Examiner has not pointed to any examples of monoclonal antibodies to this

protein having been made prior to the instant invention.

Regarding the alleged reasonable expectation of success, the tumor-specificity of TIP-2 was clearly an unexpected and surprising result. Therefore, there could not have been a reasonable expectation of success. Although TIP-2/GIPC had been previously identified and characterized (Rousset et al.; De Vries et al.), its association with malignant transformation, and breast cancer in particular, was not previously known, nor was it known that a spontaneous immune response to this protein occurs in breast cancer patients. A priori, there could not have been a reasonable expectation that the claimed invention would succeed when a basis of that invention was a surprising and unexpected discovery.

Thus, applicants submit that the cited references do not contain all the elements of the claims, and further that these references fail to establish either a motive to combine or a reasonable expectation of success. The Examiner has ignored an important element in the claims, i.e., the tumor-specific location of the TIP-2 antigen, which location was itself a surprising result. Also, the Examiner's reliance on a statement regarding a common experimental strategy to provide the alleged motivation for the specific line of research undertaken in this invention is untenable.

Applicants therefore maintain that the Examiner has failed to set forth a *prima facie* case of obviousness, and that accordingly, claims 1, 2, 8 and 10-15 satisfy the requirements for nonobviousness under 35 U.S.C. §103(a).

Claims 1-5, 8 and 10-15

The Examiner rejected claims 1, 2-5, 8 and 10-15 under 35 U.S.C. §103(a) as allegedly unpatentable over De Vries et al. (PNAS 95: 12340-12345, 1998) and Rousset et al. (Oncogene 16: 643-654, 1998) and as evidenced by the specification, and further in view of Campbell (Monoclonal Antibody Technology, Elsevier Science Publishers, pages 1-32, 1986) and Harlow et al. (Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, page 322, 1988) as applied to claims 1, 2, 8 and 10-15 above, and further in view of Adair et al. (WO 91/09967, published 7/11/91) and Green et al. (Nature Genetics 7: 13-21, 1994) of record. Claims 1, 2, 8 and 10-15 have been described above, and claims 3-5 provide embodiments of this invention wherein the antibody is chimeric, humanized and human.

In response to the Examiner's rejection of claims 1-5, 8 and 10-15, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness. In support of this position, applicants incorporate herein by reference the remarks in connection with non-obviousness set forth above in responding to the obviousness rejection of claims 1, 2, 8 and 10-15, and make the following additional remarks.

The Examiner stated that whereas the primary and secondary references do not teach a chimeric, humanized or human antibody, these deficiencies are taught by Adair et al. and Green et al. In response, applicants maintain that given there was no motivation to combine the cited references to produce monoclonal antibodies to tumor-specific TIP-2 antigen, nor did the references presage any reasonable expectation of success, it

follows that there could have been no motivation or reasonable expectation of success in making chimeric, humanized or human variants of monoclonal antibodies that bind to TIP-2 antigen specifically located on the surface of tumor cells, notwithstanding that Adair et al. teach methods of humanizing antibodies, and Green et al teach a method for making human antibodies.

Applicants therefore refute the Examiner's allegation that the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, and respectfully request that the Examiner reconsider and withdraw the rejection of claims 1-5, 8 and 10-15 under 35 U.S.C. §103(a).

Conclusion

In view of the remarks made herein, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of objection and rejection set forth in the September 26, 2002 Office Action and earnestly solicit allowance of all claims pending in the subject application.

If a telephone conference would be of assistance in advancing the prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:

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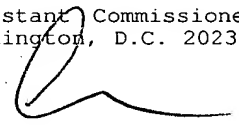

12/26/02

Alan J. Morrison
Reg. No. 37,399

Date

EXHIBIT A

MARKED-UP VERSION OF AMENDMENTS TO SPECIFICATION

Deletions from the text are indicated by square brackets; additions are indicated by underlining.

In the title:
On page 1, line 3:

[NOVEL TUMOR-ASSOCIATED MARKER] HUMAN MONOCLONAL ANTIBODIES AGAINST TUMOR-ASSOCIATED ANTIGENS

On page 11, the paragraph at lines 19-21:

The present invention provides the monoclonal antibody 27.B1 produced by the hybridoma having ATCC [Accession No. ____] Designation No. PTA-1599.

On page 12, the paragraph at lines 1-3:

The present invention provides the monoclonal antibody 27.F7 produced by the hybridoma having ATCC [Accession No. ____] Designation No. PTA-1598.

On pages 13-19, the paragraphs between page 13, line 23 and page 19, line 14:

The present invention provides a method of detecting TIP-2 antigen on the surface of cancer cells in a sample comprising: (a) contacting the sample with a antibody directed to an epitope on TIP-2 antigen or an Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma

designated [_____] PTA-1598, said antibody or Fab fragment thereof being detectably labeled, under appropriate conditions to produce an antibody 27.F7/Fab fragment-TIP-2 antigen complex comprising the detectably labeled antibody bound to any TIP-2 antigen on the surface of cells in the [sample;b] sample; b) removing any labeled antibody/Fab fragment not bound in the antibody 27.F7/Fab fragment-TIP-2 antigen complex formed in step (a); and (c) determining presence of the antibody 27.F7/Fab fragment-TIP-2 antigen complex by detecting the label of the detectably labeled antibody, presence of antibody 27.F7/Fab fragment-TIP-2 antigen complex indicating TIP-2 antigen-bearing human cancer cells in the sample.

The present invention provides a method of detecting TIP-2 antigen on the surface of cancer cells in a sample comprising: (a) contacting the sample with an antibody directed to an epitope on TIP-2 antigen which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated [_____] PTA-1598 or Fab fragment thereof, under appropriate conditions to produce an antibody 27.F7/Fab fragment-TIP-2 antigen complex comprising the antibody bound to any TIP-2 antigen on the surface of cells in the sample;
(b) removing any antibody or Fab fragment thereof not bound in the antibody 27.F7/Fab fragment-TIP-2 antigen complex formed in step (a); (c) contacting the antibody 27.F7/Fab fragment-TIP-2 antigen complex of step (b) with a second antibody which specifically binds to the antibody 27.F7/Fab fragment-TIP-2 antigen complex, said second antibody being detectably labeled, under appropriate conditions to permit the second labeled antibody to bind to the antibody 27.F7/Fab fragment-TIP-2

antigen complex; (d) removing any second labeled antibody not bound to the antibody 27.F7/Fab fragment-TIP-2 antigen complex product in (c); and (e) determining presence of the antibody 27.F7/Fab fragment-TIP-2 antigen complex bound to the second labeled antibody by detecting the label of second antibody, presence of antibody 27.F7/Fab fragment-TIP-2 antigen complex indicating TIP-2 antigen-bearing human cancer cells in the sample.

The present invention provides a method of detecting TIP-2 antigen on the surface of cancer cells in a sample comprising: (a) contacting the sample with a antibody directed to an epitope on TIP-2 antigen or an Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated [_____] PTA-1599 or Fab fragment thereof, said antibody or Fab fragment [therof] thereof being detectably labeled, under appropriate conditions to produce an antibody 27.B1/Fab fragment-TIP-2 antigen complex comprising the detectably labeled antibody bound to any TIP-2 antigen on the surface of cells in the sample; (b) removing any labeled antibody not bound in the antibody 27.B1-TIP-2 antigen complex formed in step (a); and (c) determining presence of the antibody 27.B1/Fab fragment-TIP-2 antigen complex by detecting the label of the detectably labeled antibody, presence of antibody 27.B1/Fab fragment-TIP-2 antigen complex indicating TIP-2 antigen-bearing human cancer cells in the sample.

The present invention provides a method of detecting TIP-2 antigen on the surface of cancer cells in a sample comprising: (a) contacting the sample with an antibody directed to an epitope on TIP-2 antigen or an Fab

fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated [_____] PTA-1599, or Fab fragment thereof under appropriate conditions to produce an antibody 27.B1/Fab fragment-TIP-2 antigen complex comprising the antibody bound to any TIP-2 antigen on the surface of cells in the sample; (b) removing any antibody/Fab fragment thereof not bound in the antibody 27.B1/Fab fragment-TIP-2 antigen complex formed in step (a); (c) contacting the antibody 27.B1/Fab fragment-TIP-2 antigen complex of step (b) with a second antibody which specifically binds to the antibody 27.B1/Fab fragment-TIP-2 antigen complex, said second antibody being detectably labeled, under appropriate conditions to permit the second labeled antibody to bind to the antibody 27.B1/Fab fragment-TIP-2 antigen complex; (d) removing any second labeled antibody not bound to the antibody 27.B1/Fab fragment-TIP-2 antigen complex product in (c); and (e) determining presence of the antibody 27.B1/Fab fragment-TIP-2 antigen complex bound to the second labeled antibody by detecting the label of second antibody, presence of antibody 27.B1/Fab fragment-TIP-2 antigen complex indicating TIP-2 antigen-bearing human cancer cells in the sample.

The present invention provides a method for diagnosing cancer in a subject by detecting TIP-2 antigen-bearing cancer cells which comprises: (a) obtaining a sample of the subject's peripheral blood; (b) [cntacting] contacting the sample with an antibody directed to an epitope on TIP-2 antigen or an Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated [_____] PTA-1598 or an Fab fragment thereof, said antibody being

detectably labeled, under appropriate conditions to produce an antibody 27.F7/Fab fragment-TIP-2 antigen complex comprising the detectably labeled antibody bound to any TIP-2 antigen on the surface of cells in the sample; (c) removing any labeled antibody/Fab fragment not bound in the antibody 27.F7/Fab fragment-TIP-2 antigen complex formed in step (b); and (d) determining presence of the antibody 27.F7/Fab fragment-TIP-2 antigen complex by detecting the label of the detectably labeled antibody, presence of antibody 27.F7/Fab fragment-TIP-2 antigen complex indicating diagnosis of cancer in the subject.

The present invention provides a method for diagnosing cancer in a subject by detecting TIP-2 antigen-bearing cancer cells which comprises: (a) obtaining a sample of the subject's peripheral blood; (b) contacting the sample with an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated [_____] PTA-1598 or Fab fragment thereof, under appropriate conditions to produce an antibody 27.F7/Fab fragment-TIP-2 antigen complex comprising the antibody bound to any TIP-2 antigen on the surface of cells in the sample; (c) removing any antibody/Fab fragment not bound in the antibody 27.F7/Fab fragment-TIP-2 antigen complex formed in step (b); (d) contacting the antibody 27.F7/Fab fragment-TIP-2 antigen complex of step (c) with a second antibody which specifically binds to the antibody 27.F7/Fab fragment-TIP-2 antigen complex, said second antibody being detectably labeled, under appropriate conditions to permit the second labeled antibody to bind to the antibody 27.F7/Fab fragment-TIP-2 antigen complex; (e) removing any second labeled antibody

not bound to the antibody 27.F7/Fab fragment-TIP-2 antigen complex product in (d); and (f) determining presence of the antibody 27.F7/Fab fragment-TIP-2 antigen complex bound to the second labeled antibody by detecting the label of second antibody, presence of antibody 27.F7/Fab fragment-TIP-2 antigen complex indicating diagnosis of cancer in the subject.

The present invention provides a method for diagnosing cancer in a subject by detecting TIP-2 antigen-bearing cancer cells which comprises: (a) obtaining a sample of the subject's peripheral blood; (b) contacting the sample with an antibody directed to an epitope on TIP-2 antigen or an Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated [_____] PTA-1599, said antibody being detectably labeled, under appropriate conditions to produce an antibody 27.B1/Fab fragment-TIP-2 antigen complex comprising the detectably labeled antibody bound to any TIP-2 antigen on the surface of cells in the sample; (c) removing any labeled antibody/Fab fragment not bound in the antibody 27.B1/Fab fragment-TIP-2 antigen complex formed in step (b); and (d) determining presence of the antibody 27.B1/Fab fragment-TIP-2 antigen complex by detecting the label of the detectably labeled antibody, presence of antibody 27.B1/Fab fragment-TIP-2 antigen complex indicating diagnosis of cancer in the subject.

The present invention provides a method for diagnosing cancer in a subject by detecting TIP-2 antigen-bearing cancer cells which comprises: (a) obtaining a sample of the subject's peripheral blood; (b) contacting the sample with an antibody directed to an epitope on TIP-2 antigen

or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1/Fab fragment produced by the hybridoma designated [_____] PTA-1599 or Fab fragment thereof, under appropriate conditions to produce an antibody 27.B1/Fab fragment-TIP-2 antigen complex comprising the antibody bound to any TIP-2 antigen on the surface of cells in the sample; (c) removing any antibody/Fab fragment not bound in the antibody 27.B1/Fab fragment-TIP-2 antigen complex formed in step (b); (d) contacting the antibody 27.B1/Fab fragment-TIP-2 antigen complex of step (c) with a second antibody which specifically binds to the antibody 27.B1/Fab fragment-TIP-2 antigen complex, said second antibody being detectably labeled, under appropriate conditions to permit the second labeled antibody to bind to the antibody 27.B1/Fab fragment-TIP-2 antigen complex; (e) removing any second labeled antibody not bound to the antibody 27.B1/Fab fragment-TIP-2 antigen complex product in (d); and (f) determining presence of the antibody 27.B1/Fab fragment-TIP-2 antigen complex bound to the second labeled antibody by detecting the label of second antibody, presence of antibody 27.B1/Fab fragment-TIP-2 antigen complex indicating diagnosis of cancer in the subject.

The present invention provides an in vivo method for diagnosing cancer in a subject by detecting TIP-2 antigen-bearing cancer cells which comprises: (a) administering to the subject an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated [_____] PTA-1598, said antibody being detectably labeled, under appropriate conditions to bind the antibody to TIP-2 antigen on the

surface of any cells in the subject; and (b) determining presence of the detectably labeled antibody 27.F7 bound to the surface of cells in the subject, presence of detectably labeled antibody 27.F7 bound to cells indicating diagnosis of cancer in the subject.

The present invention provides an in vivo method for diagnosing cancer in a subject by detecting TIP-2 antigen-bearing cancer cells which comprises: (a) administering to the subject an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated [_____] PTA-1599, said antibody/Fab fragment being detectably labeled, under appropriate conditions to bind the antibody to TIP-2 antigen on the surface of any cells in the subject; and (b) determining presence of the detectably labeled antibody/Fab fragment 27.B1 bound to the surface of cells in the subject, presence of detectably labeled antibody 27.F7/Fab fragment bound to cells indicating diagnosis of cancer in the subject.

On pages 20-21, the paragraph between page 20, line 33 and page 21, line 15:

The present invention provides a method for immunohistochemical screening of a tissue section from a tumor sample for the presence of TIP-2 antigen bearing cancer cells which comprises: (a) contacting the tissue section from the tumor sample with a detectably labeled antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated [_____] PTA-1598, said antibody/Fab fragment

being detectably labeled, under appropriate conditions to produce an antibody 27.F7/Fab fragment-TIP-2 antigen complex comprising the detectably labeled antibody bound to any TIP-2 antigen on the surface of cells in the tissue section; (a) removing any labeled antibody/Fab fragment not bound in the antibody 27.F7/Fab fragment-TIP-2 antigen complex formed in step (a); and (b) determining presence of the antibody 27.F7/Fab fragment-TIP-2 antigen complex by detecting the label of the detectably labeled antibody, presence of antibody 27.F7/Fab fragment-TIP-2 antigen complex indicating TIP-2 antigen-bearing human cancer cells in the sample.

On pages 21-25, the paragraphs between page 21, line 27 and page 25, line 35:

The present invention provides a method for detecting the presence of TIP-2 antigen in biological fluid comprising: [(a)contacting] (a) contacting a sample of the biological fluid with [a] an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated [_____] PTA-1598, said antibody being detectably labeled, under appropriate conditions to produce an antibody 27.F7/Fab fragment-TIP-2 antigen complex comprising the detectably labeled antibody bound to any TIP-2 antigen on the surface of cells in the sample; [(c)] (b) removing any labeled antibody not bound in the antibody 27.F7/Fab fragment-TIP-2 antigen complex formed in step (a); and [(d)] (c) determining presence of the antibody 27.F7/Fab fragment-TIP-2 antigen complex by detecting the label of the detectably labeled antibody, presence of antibody 27.F7/Fab fragment-TIP-2 antigen

complex indicating TIP-2 antigen-bearing human cancer cells in the biological fluid.

The present invention provides a method for detecting the presence of TIP-2 antigen in biological fluid comprising: [(a)contacting] (a) contacting a sample of the biological fluid with a antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated [_____] PTA-1599, said antibody being detectably labeled, under appropriate conditions to produce an antibody 27.B1/Fab fragment-TIP-2 antigen complex comprising the detectably labeled antibody bound to any TIP-2 antigen on the surface of cells in the sample; [(c)] (b) removing any labeled antibody not bound in the antibody 27.B1/Fab fragment-TIP-2 antigen complex formed in step (a); and [(d)] (c) determining presence of the antibody 27.B1/Fab fragment-TIP-2 antigen complex by detecting the label of the detectably labeled antibody, presence of antibody 27.B1/Fab fragment-TIP-2 antigen complex indicating TIP-2 antigen-bearing human cancer cells in the biological fluid.

The present invention provides a method for immunohistochemical screening of tissue sections from a tumor sample for the presence of TIP-2 antigen-bearing cancer cells which comprises: (a) contacting the tissue section from the tumor sample with a detectably labeled antibody/Fab fragment directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated [_____] PTA-1599, said antibody being detectably labeled, under appropriate conditions to bind the antibody to TIP-2 antigen on the surface of any

cells in the sample; [and (b)removing] (b) removing any labeled antibody not bound to the cells in the sample; and (c) determining presence of antibody 27.B1 bound to the cells in the sample, presence of antibody 27.B1 bound to cells indicating TIP-2 antigen-bearing cancer cells in the tumor sample.

The present invention provides a method for monitoring progression of cancer, wherein cancer cells are TIP-2 antigen-bearing cancer cells, in a subject comprising: (a) administering to a subject diagnosed with cancer an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated [_____] PTA-1598, said antibody being detectably labeled, under appropriate conditions to bind the antibody to TIP-2 antigen on the surface of any cells in the subject; (b) determining presence of detectably labeled antibody 27.F7/Fab fragment bound to the surface of cells in the subject [according to the] according to the above-described method of detecting TIP-2 antigen on the surface of cancer cells in a sample; (c) comparing the presence of detectably labeled antibody/Fab fragment 27.F7 bound to cells in step (b) with the presence of detectably labeled antibody 27.F7 bound to cells at (i) diagnosis time or (ii) after treatment, wherein a greater presence of detectably labeled antibody 27.F7/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment, indicates progression of the cancer in the subject and a lesser presence of detectably labeled antibody 27.F7/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment indicates regression of the cancer in the subject.

The present invention provides a method for monitoring progression of cancer, wherein cancer cells are TIP-2 antigen-bearing cancer cells, in a subject comprising: (a) administering to a subject diagnosed with cancer an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated [_____] PTA-1599, said antibody/Fab fragment being detectably labeled, under appropriate conditions to bind the antibody to TIP-2 antigen on the surface of any cells in the subject; (b) determining presence of detectably labeled antibody 27.B1/Fab fragment bound to the surface of cells in the subject [the] according to the above-described method for detecting TIP-2 antigen on the surface of cancer cells in a sample; (c) comparing the presence of detectably labeled antibody/Fab fragment 27.B1 bound to cells in step (b) with the presence of detectably labeled antibody 27.B1/Fab fragment bound to cells at (i) diagnosis time or (ii) after treatment, wherein a greater presence of detectably labeled antibody 27.B1/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment, indicates progression of the cancer in the subject and a lesser presence of detectably labeled antibody 27.B1/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment indicates regression of the cancer in the subject.

The present invention provides a method for monitoring progression of cancer, wherein cancer cells are TIP-2 antigen-bearing cancer cells, in a subject comprising: (a) administering to a subject diagnosed with cancer an antibody directed to an epitope on TIP-2 antigen or an

Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated [_____] PTA-1598, said antibody/Fab fragment being detectably labeled, under appropriate conditions to bind the antibody to TIP-2 antigen on the surface of any cells in the subject; (b) determining quantity of detectably labeled antibody 27.F7/Fab fragment bound to the surface of cells in the subject according to the above-described method for detecting TIP-2 antigen on the surface of cancer cells in a sample; [(c)comparing] (c) comparing the quantity of detectably labeled antibody 27.F7/Fab fragment bound to cells in step (b) with the presence of detectably labeled antibody 27.F7/Fab fragment bound to cells at (i) diagnosis time or (ii) after treatment, wherein a greater quantity of detectably labeled antibody 27.F7/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment, indicates progression of the cancer in the subject and a lesser quantity of detectably labeled antibody 27.F7/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment indicates regression of the cancer in the subject.

The present invention provides a method for monitoring progression of cancer, wherein cancer cells are TIP-2 antigen-bearing cancer cells, in a subject comprising: (a) administering to a subject diagnosed with the cancer an antibody directed to an epitope on TIP-2 antigen or an Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated [_____] PTA-1599, said antibody/Fab fragment being detectably labeled, under appropriate conditions to bind the antibody to TIP-2 antigen on the surface of any cells in the subject; (b) determining quantity of

detectably labeled antibody 27.B1/Fab fragment bound to the surface of cells in the subject according to the above-described method [of -------]; and (c) comparing the quantity of detectably labeled antibody 27.B1/Fab fragment bound to cells in step (b) with the presence of detectably labeled antibody 27.B1 bound to cells at (i) diagnosis time or (ii) after treatment, wherein a greater quantity of detectably labeled antibody 27.B1/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment, indicates progression of the cancer in the subject and a lesser quantity of detectably labeled antibody 27.B1/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment indicates regression of the cancer in the subject.

On page 39, the paragraph between lines 14-23:

This invention also provides human hybridoma fusion partner cell line heteromyeloma B6B11, and human hybridoma fusion partner cell line trioma MFP-2. These hybridoma cell lines were deposited on March 17, 1998 with the American Type Culture Collection (ATCC), [12301 Parklawn Drive, Rockville, Maryland 20852, U.S.S.] 10801 University Boulevard, Manassas, VA 20110-2209, U.S.A., under the [provision] provisions of the Budapest Treaty for the International Recognition of the Deposit of [Microorganism] Microorganisms for the Purposes of Patent Procedure. These [hybridoma] hybridomas have been accorded [with] ATCC [Accession] Designation Nos. HB-12481 and HB-12482 respectively.

On pages 56-57, the paragraphs between page 56, line 13 and page 57, line 4:

The present invention provides a monoclonal antibody which specifically binds and forms a complex with TIP-2 antigen located on the surface of human cancer cells, the TIP-2 antigen being an antigen to which monoclonal antibody 27.B1 specifically binds. According to certain embodiments of the present invention, the monoclonal antibody of the invention is a murine monoclonal antibody, a chimaeric monoclonal antibody, a humanized monoclonal antibody, or a human monoclonal antibody. In an embodiment of the present invention, the monoclonal antibody of the invention is capable of binding to the epitope which is specifically recognized by monoclonal antibody 27.B1 produced by the hybridoma having ATCC [Accession No._____] Designation No. PTA-1599.

The present invention provides the monoclonal antibody 27.B1 produced by the hybridoma having ATCC [Accession No._____] Designation No. PTA-1599.

The present invention provides a hybridoma cell producing the monoclonal antibody of this invention. In an embodiment of the invention, the hybridoma cell has ATCC [Accession No._____] Designation No. PTA-1599.

Hybridoma 27.B1 was deposited on March 28, 2000 with the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, [Va] VA, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of [Microorganism] Microorganisms for the Purposes of Patent Procedure. 27.B1 was accorded ATCC [Accession Number_____] Designation No. PTA-1599.

On pages 57-58, the paragraphs between page 57, line 27 and

page 58, line 19:

The present invention provides a monoclonal antibody which specifically binds and forms a complex with TIP-2 antigen located on the surface of human cancer cells, the TIP-2 antigen being an antigen to which monoclonal antibody 27.F7 specifically binds. According to certain embodiments of the present invention, the monoclonal antibody of the invention is a murine monoclonal antibody, a chimaeric monoclonal antibody, a humanized monoclonal antibody, or a human monoclonal antibody. In an embodiment of the present invention, the monoclonal antibody of the invention is capable of binding to the epitope which is specifically recognized by monoclonal antibody 27.F7 produced by the hybridoma having ATCC [Accession No._____] Designation No. PTA-1598.

The present invention provides the monoclonal antibody 27.F7 produced by the hybridoma having ATCC [Accession No._____] Designation No. PTA-1598.

The present invention provides a hybridoma cell producing the monoclonal antibody of this invention. In an embodiment of the invention, the hybridoma cell has ATCC [Accession No._____] Designation No. PTA-1598.

Hybridoma 27.F7 was deposited on March 28, 2000 with the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, [Va] VA, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of [Microorganism] Microorganisms for the Purposes of Patent Procedure. 27.F7 was accorded ATCC [Accession Number_____] Designation No. PTA-1598.

On pages 62-63, the paragraph between page 62, line 23 and page 63, line 2:

> The present invention provides a method of detecting TIP-2 antigen on the surface of cancer cells in a sample comprising: (a) contacting the sample with a antibody directed to an epitope on TIP-2 antigen or an Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated [_____] PTA-1598, said antibody or Fab fragment thereof being detectably labeled, under appropriate conditions to produce an antibody 27.F7/Fab fragment-TIP-2 antigen complex comprising the detectably labeled antibody bound to any TIP-2 antigen on the surface of cells in the sample; [b)removing] (b) removing any labeled antibody/Fab fragment not bound in the antibody 27.F7/Fab fragment-TIP-2 antigen complex formed in step (a); and (c) determining presence of the antibody 27.F7/Fab fragment-TIP-2 antigen complex by detecting the label of the detectably labeled antibody, presence of antibody 27.F7/Fab fragment-TIP-2 antigen complex indicating TIP-2 antigen-bearing human cancer cells in the sample.

On page 64, the paragraph between lines 1-27:

> The present invention provides a method of detecting TIP-2 antigen on the surface of cancer cells in a sample comprising: (a) contacting the sample with an antibody directed to an epitope on TIP-2 antigen which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated [_____] PTA-1598 or Fab fragment thereof, under appropriate conditions to produce an antibody 27.F7/Fab fragment-TIP-2 antigen complex

comprising the antibody bound to any TIP-2 antigen on the surface of cells in the sample; (b) removing any antibody or Fab fragment thereof not bound in the antibody 27.F7/Fab fragment-TIP-2 antigen complex formed in step (a); (c) contacting the antibody 27.F7/Fab fragment-TIP-2 antigen complex of step (b) with a second antibody which specifically binds to the antibody 27.F7/Fab fragment-TIP-2 antigen complex, said second antibody being detectably labeled, under appropriate conditions to permit the second labeled antibody to bind to the antibody 27.F7/Fab fragment-TIP-2 antigen complex; (d) removing any second labeled antibody not bound to the antibody 27.F7/Fab fragment-TIP-2 antigen complex product in (c); and (e) determining presence of the antibody 27.F7/Fab fragment-TIP-2 antigen complex bound to the second labeled antibody by detecting the label of second antibody, presence of antibody 27.F7/Fab fragment-TIP-2 antigen complex indicating TIP-2 antigen-bearing human cancer cells in the sample.

On pages 65-66, the paragraph between page 65, line 25 and page 66, line 4:

The present invention provides a method of detecting TIP-2 antigen on the surface of cancer cells in a sample comprising: (a) contacting the sample with [a] an antibody directed to an epitope on TIP-2 antigen or an Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated [_____] PTA-1599 or Fab fragment thereof, said antibody or Fab fragment thereof being detectably labeled, under appropriate conditions to produce an antibody 27.B1/Fab fragment-TIP-2 antigen complex comprising the detectably labeled antibody bound to any

TIP-2 antigen on the surface of cells in the sample; (b) removing any labeled antibody not bound in the antibody 27.B1-TIP-2 antigen complex formed in step (a); and (c) determining presence of the antibody 27.B1/Fab fragment-TIP-2 antigen complex by detecting the label of the detectably labeled antibody, presence of antibody 27.B1/Fab fragment-TIP-2 antigen complex indicating TIP-2 antigen-bearing human cancer cells in the sample.

On page 67, the paragraph between lines 4-30:

The present invention provides a method of detecting TIP-2 antigen on the surface of cancer cells in a sample comprising: (a) contacting the sample with an antibody directed to an epitope on TIP-2 antigen or an Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated [_____] PTA-1599, or Fab fragment thereof under appropriate conditions to produce an antibody 27.B1/Fab fragment-TIP-2 antigen complex comprising the antibody bound to any TIP-2 antigen on the surface of cells in the sample; (b) removing any antibody/Fab fragment thereof not bound in the antibody 27.B1/Fab fragment-TIP-2 antigen complex formed in step (a); (c) contacting the antibody 27.B1/Fab fragment-TIP-2 antigen complex of step (b) with a second antibody which specifically binds to the antibody 27.B1/Fab fragment-TIP-2 antigen complex, said second antibody being detectably labeled, under appropriate conditions to permit the second labeled antibody to bind to the antibody 27.B1/Fab fragment-TIP-2 antigen complex; (d) removing any second labeled antibody not bound to the antibody 27.B1/Fab fragment-TIP-2 antigen complex product in (c); and (e) determining presence of the antibody

27.B1/Fab fragment-TIP-2 antigen complex bound to the second labeled antibody by detecting the label of second antibody, presence of antibody 27.B1/Fab fragment-TIP-2 antigen complex indicating TIP-2 antigen-bearing human cancer cells in the sample.

On pages 68-69, the paragraph between page 68, line 28 and page 69, line 8:

The present invention provides a method for diagnosing cancer in a subject by detecting TIP-2 antigen-bearing cancer cells which comprises: (a) obtaining a sample of the subject's peripheral blood; (b) contacting the sample with an antibody directed to an epitope on TIP-2 antigen or an Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated [_____] PTA-1598 or an Fab fragment thereof, said antibody being detectably labeled, under appropriate conditions to produce an antibody 27.F7/Fab fragment-TIP-2 antigen complex comprising the detectably labeled antibody bound to any TIP-2 antigen on the surface of cells in the sample; (c) removing any labeled antibody/Fab fragment not bound in the antibody 27.F7/Fab fragment-TIP-2 antigen complex formed in step (b); and (d) determining presence of the antibody 27.F7/Fab fragment-TIP-2 antigen complex by detecting the label of the detectably labeled antibody, presence of antibody 27.F7/Fab fragment-TIP-2 antigen complex indicating diagnosis of cancer in the subject.

On page 70, the paragraph between lines 4-30:

The present invention provides a method for diagnosing cancer in a subject by detecting TIP-2 antigen-bearing cancer cells which [comprises:(a)] comprises: (a)

obtaining a sample of the subject's peripheral blood; (b) contacting the sample with an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated [_____] PTA-1598 or Fab fragment thereof, under appropriate conditions to produce an antibody 27.F7/Fab fragment-TIP-2 antigen complex comprising the antibody bound to any TIP-2 antigen on the surface of cells in the sample; (c) removing any antibody/Fab fragment not bound in the antibody 27.F7/Fab fragment-TIP-2 antigen complex formed in step (b); (d) contacting the antibody 27.F7/Fab fragment-TIP-2 antigen complex of step (c) with a second antibody which specifically binds to the antibody 27.F7/Fab fragment-TIP-2 antigen complex, said second antibody being detectably labeled, under appropriate conditions to permit the second labeled antibody to bind to the antibody 27.F7/Fab fragment-TIP-2 antigen complex; (e) removing any second labeled antibody not bound to the antibody 27.F7/Fab fragment-TIP-2 antigen complex product in (d); and (f) determining presence of the antibody 27.F7/Fab fragment-TIP-2 antigen complex bound to the second labeled antibody by detecting the label of second antibody, presence of antibody 27.F7/Fab fragment-TIP-2 antigen complex indicating diagnosis of cancer in the subject.

On pages 71-72, the paragraph between page 71, line 26 and page 72, line 6:

The present invention provides a method for diagnosing cancer in a subject by detecting TIP-2 antigen-bearing cancer cells which comprises: (a) obtaining a sample of the subject's peripheral blood; (b) contacting the sample with an antibody directed to an epitope on TIP-2 antigen

or an Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated [_____] PTA-1599, said antibody being detectably labeled, under appropriate conditions to produce an antibody 27.B1/Fab fragment-TIP-2 antigen complex comprising the detectably labeled antibody bound to any TIP-2 antigen on the surface of cells in the sample; [(c)removing] (c) removing any labeled antibody/Fab fragment not bound in the antibody 27.B1/Fab fragment-TIP-2 antigen complex formed in step (b); and (d) determining presence of the antibody 27.B1/Fab fragment-TIP-2 antigen complex by detecting the label of the detectably labeled antibody, presence of antibody 27.B1/Fab fragment-TIP-2 antigen complex indicating diagnosis of cancer in the subject.

On page 73, the paragraph between lines 4-30:

The present invention provides a method for diagnosing cancer in a subject by detecting TIP-2 antigen-bearing cancer cells which comprises: (a) obtaining a sample of the subject's peripheral blood; (b) contacting the sample with an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1/Fab fragment produced by the hybridoma designated [_____] PTA-1599 or Fab fragment thereof, under appropriate conditions to produce an antibody 27.B1/Fab fragment-TIP-2 antigen complex comprising the antibody bound to any TIP-2 antigen on the surface of cells in the sample; (c) removing any antibody/Fab fragment not bound in the antibody 27.B1/Fab fragment-TIP-2 antigen complex formed in step (b); (d) contacting the antibody 27.B1/Fab fragment-TIP-2 antigen complex of step (c) with a second antibody which

specifically binds to the antibody 27.B1/Fab fragment-TIP-2 antigen complex, said second antibody being detectably labeled, under appropriate conditions to permit the second labeled antibody to bind to the antibody 27.B1/Fab fragment-TIP-2 antigen complex; (e) removing any second labeled antibody not bound to the antibody 27.B1/Fab fragment-TIP-2 antigen complex product in (d); and (f) determining presence of the antibody 27.B1/Fab fragment-TIP-2 antigen complex bound to the second labeled antibody by detecting the label of second antibody, presence of antibody 27.B1/Fab fragment-TIP-2 antigen complex indicating diagnosis of cancer in the subject.

On pages 74-75, the paragraph between page 74, line 26 and page 75, line 2:

The present invention provides an <u>in vivo</u> method for diagnosing cancer in a subject by detecting TIP-2 antigen-bearing cancer cells which comprises: (a) administering to the subject an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated [_____] <u>PTA-1598</u>, said antibody being detectably labeled, under appropriate conditions to bind the antibody to TIP-2 antigen on the surface of any cells in the subject; and (b) determining presence of the detectably labeled antibody 27.F7 bound to the surface of cells in the subject, presence of detectably labeled antibody 27.F7 bound to cells indicating diagnosis of cancer in the subject.

On pages 75-76, the paragraph between page 75, line 35 and page 76, line 10:

The present invention provides an in vivo method for diagnosing cancer in a subject by detecting TIP-2 antigen-bearing cancer cells which comprises: (a) administering to the subject an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated [_____] PTA-1599, said antibody/Fab fragment being detectably labeled, under appropriate conditions to bind the antibody to TIP-2 antigen on the surface of any cells in the subject; and (b) determining presence of the detectably labeled antibody/Fab fragment 27.B1 bound to the surface of cells in the subject, presence of detectably labeled antibody 27.F7/Fab fragment bound to cells indicating diagnosis of cancer in the subject.

On page 81, the paragraph between lines 12-31:

The present invention provides a method for immunohistochemical screening of a tissue section from a tumor sample for the presence of TIP-2 antigen bearing cancer cells which comprises: (a) contacting the tissue section from the tumor sample with an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated [_____] PTA-1598, said antibody/Fab fragment being detectably labeled, under appropriate conditions to produce an antibody 27.F7/Fab fragment-TIP-2 antigen complex comprising the detectably labeled antibody bound to any TIP-2 antigen on the surface of cells in the tissue section; (a) removing any labeled antibody/Fab fragment not bound in the antibody 27.F7/Fab fragment-TIP-2 antigen complex formed

in step (a); and (b) determining presence of the antibody 27.F7/Fab fragment-TIP-2 antigen complex by detecting the label of the detectably labeled antibody, presence of antibody 27.F7/Fab fragment-TIP-2 antigen complex indicating TIP-2 antigen-bearing human cancer cells in the sample.

On pages 82-83, the paragraphs between page 72, line 35 and page 83, line 14:

In an embodiment of this invention the monoclonal antibody directed to the epitope on TIP-2 antigen is human monoclonal antibody 27.F7 directed to an epitope on TIP-2 antigen, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated [_____] PTA-1598.

In an embodiment of this invention the monoclonal antibody directed to the epitope on TIP-2 antigen is human monoclonal antibody 27.B1 directed to an epitope on TIP-2 antigen, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated [_____] PTA-1599.

In an embodiment of this invention the monoclonal antibody directed to the epitope of TIP-2 antigen is murine monoclonal antibody directed to an epitope on TIP-2 antigen, which epitope is recognized by monoclonal antibody produced by the hybridoma designated [_____] PTA-1599.

On page 84, the paragraph between lines 10-27:

The present invention provides a method for detecting the presence of TIP-2 antigen in biological fluid comprising: [(a)contacting] (a) contacting a sample of the biological fluid with a antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated [_____] PTA-1598, said antibody being detectably labeled, under appropriate conditions to produce an antibody 27.F7/Fab fragment-TIP-2 antigen complex comprising the detectably labeled antibody bound to any TIP-2 antigen on the surface of cells in the sample; (c) removing any labeled antibody not bound in the antibody 27.F7/Fab fragment-TIP-2 antigen complex formed in step (a); and (d) determining presence of the antibody 27.F7/Fab fragment-TIP-2 antigen complex by detecting the label of the detectably labeled antibody, presence of antibody 27.F7/Fab fragment-TIP-2 antigen complex indicating TIP-2 antigen-bearing human cancer cells in the biological fluid.

On page 85, the paragraphs between lines 19-29:

In an embodiment of this invention the monoclonal antibody directed to the epitope on TIP-2 antigen is human monoclonal antibody 27.F7 directed to an epitope on TIP-2 antigen, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated [_____] PTA-1598.

In an embodiment of this invention the monoclonal antibody directed to the epitope on TIP-2 antigen is human monoclonal antibody 27.B1 directed to an epitope on TIP-2 antigen, which epitope is recognized by monoclonal

antibody 27.B1 produced by the hybridoma designated [_____] PTA-1599.

On page 86, the paragraph between lines 1-17:

The present invention provides a method for immunohistochemical screening of tissue sections from a tumor sample for the presence of TIP-2 antigen-bearing cancer cells which comprises: (a) contacting the tissue section from the tumor sample with a detectably labeled antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated [_____] PTA-1599, said antibody being detectably labeled, under appropriate conditions to bind the antibody to TIP-2 antigen on the surface of any cells in the sample; [and] (b) removing any labeled antibody not bound to the cells in the sample; and (c) determining presence of antibody 27.B1 bound to the cells in the sample, presence of antibody 27.B1 bound to cells indicating TIP-2 antigen-bearing cancer cells in the tumor sample.

On page 87, the paragraph between lines 8-32:

The present invention provides a method for monitoring progression of cancer, wherein cancer cells are TIP-2 antigen-bearing cancer cells, in a subject comprising: (a) administering to a subject diagnosed with cancer an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated [_____] PTA-1598, said antibody being detectably labeled, under appropriate conditions to bind

the antibody to TIP-2 antigen on the surface of any cells in the subject; (b) determining presence of detectably labeled antibody 27.F7/Fab fragment bound to the surface of cells in the subject according to the [according to the] instant method [of claim 23]; and (c) comparing the presence of detectably labeled antibody/Fab fragment 27.F7 bound to cells in step (b) with the presence of detectably labeled antibody 27.F7 bound to cells at (i) diagnosis time or (ii) after treatment, wherein a greater presence of detectably labeled antibody 27.F7/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment, indicates progression of the cancer in the subject and a lesser presence of detectably labeled antibody 27.F7/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment indicates regression of the cancer in the subject.

On pages 88-89, the paragraphs between page 88, line 25 and page 89, line 11:

The present invention provides a method for monitoring progression of cancer, wherein cancer cells are TIP-2 antigen-bearing cancer cells, in a subject comprising: (a) administering to a subject diagnosed with cancer an antibody directed to an epitope on TIP-2 antigen or Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated [_____] PTA-1599, said antibody/Fab fragment being detectably labeled, under appropriate conditions to bind the antibody to TIP-2 antigen on the surface of any cells in the subject; (b) determining presence of detectably labeled antibody 27.B1/Fab fragment bound to the surface of cells in the subject according to the

[according to the] instant method [of claim 23]; and (c) comparing the presence of detectably labeled antibody/Fab fragment 27.B1 bound to cells in step (b) with the presence of detectably labeled antibody 27.B1/Fab fragment bound to cells at (i) diagnosis time or (ii) after treatment, wherein a greater presence of detectably labeled antibody 27.B1/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment, indicates progression of the cancer in the subject and a lesser presence of detectably labeled antibody 27.B1/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment indicates regression of the cancer in the subject.

On page 90, the paragraph between lines 4-28:

The present invention provides a method for monitoring progression of cancer, wherein cancer cells are TIP-2 antigen-bearing cancer cells, in a subject comprising: (a) administering to a subject diagnosed with cancer an antibody directed to an epitope on TIP-2 antigen or an Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.F7 produced by the hybridoma designated [_____] PTA-1598, said antibody/Fab fragment being detectably labeled, under appropriate conditions to bind the antibody to TIP-2 antigen on the surface of any cells in the subject; (b) determining quantity of detectably labeled antibody 27.F7/Fab fragment bound to the surface of cells in the subject according to the [according to the] instant method [of claim 23; (c)comparing]; and (c) comparing the quantity of detectably labeled antibody 27.F7/Fab fragment bound to cells in step (b) with the presence of detectably labeled antibody 27.F7/Fab fragment bound to cells at (i)

diagnosis time or (ii) after treatment, wherein a greater quantity of detectably labeled antibody 27.F7/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment, indicates progression of the cancer in the subject and a lesser quantity of detectably labeled antibody 27.F7/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment indicates regression of the cancer in the subject.

On page 92, the paragraph between lines 11-35:

The present invention provides a method for monitoring progression of cancer, wherein cancer cells are TIP-2 antigen-bearing cancer cells, in a subject comprising: (a) administering to a subject diagnosed with the cancer an antibody directed to an epitope on TIP-2 antigen or an Fab fragment thereof, which epitope is recognized by monoclonal antibody 27.B1 produced by the hybridoma designated [_____] PTA-1599, said antibody/Fab fragment being detectably labeled, under appropriate conditions to bind the antibody to TIP-2 antigen on the surface of any cells in the subject; (b) determining quantity of detectably labeled antibody 27.B1/Fab fragment bound to the surface of cells in the subject according to the [according to the] instant method [of claim 27]; and (c) comparing the quantity of detectably labeled antibody 27.B1/Fab fragment bound to cells in step (b) with the presence of detectably labeled antibody 27.B1 bound to cells at (i) diagnosis time or (ii) after treatment, wherein a greater quantity of detectably labeled antibody 27.B1/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment, indicates progression of the cancer in the subject and a lesser

quantity of detectably labeled antibody 27.B1/Fab fragment bound to cells in step (b) than at (i) diagnosis time or (ii) after treatment indicates regression of the cancer in the subject.

EXHIBIT B

MARKED-UP VERSION OF AMENDMENTS TO CLAIMS

Deletions from the text are indicated by square brackets; additions are indicated by underlining.

Claim 6:

6. [A] The monoclonal antibody of claim 1 which binds to the same [epitope] domain of TIP-2 as does monoclonal antibody 27.B1.

Claim 16:

16. [A] The monoclonal antibody of claim 1 which binds to the same [epitope] domain of TIP-2 as does monoclonal antibody 27.F7.

ATCC

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BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF
THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3
AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

To: (Name and Address of Depositor or Attorney)

Cooper & Dunham LLP
Attn: John P. White, Esq.
1185 Avenue of the Americas
New York, NY 10036

Deposited on Behalf of: The Trustees of Columbia University in the City of New York

Identification Reference by Depositor:	**Patent Deposit Designation**
Heterohybridoma (human x [human x (human x mouse)]): 27.F7 (Ref: Docket or Case No.: 0575/60240/JPW/EMW/MMM)	PTA-1598
Heterohybridoma (human x [human x (mouse x human)]): 27.B1 (Ref: Docket or Case No.: 0575/60240/JPW/EMW/MMM)	PTA-1599

The deposits were accompanied by: __ a scientific description _ a proposed taxonomic description indicated above. The deposits were received March 29, 2000 by this International Depository Authority and have been accepted.

AT YOUR REQUEST: X We will inform you of requests for the strains for 30 years.

The strains will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strains, and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strains.

If the cultures should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace them with living cultures of the same.

The strains will be maintained for a period of at least 30 years from date of deposit, or five years after the most recent request for a sample, whichever is longer. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the cultures cited above was tested April 11, 2000. On that date, the cultures were viable.

International Depository Authority: American Type Culture Collection, Manassas, VA 20110-2209 USA.

Signature of person having authority to represent ATCC:

Barbara E. Coupé

Barbara E. Coupé, Administrator, Patent Depository

Date: April 12, 2000

cc: